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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/355,210	07/12/2000	Raffaello Giorgi	515-4167	6135

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EXAMINER	
LUKTON, DAVID	
ART UNIT	PAPER NUMBER
1653	23

DATE MAILED: 05/19/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/355,210	GIORGI ET AL.	
	Examiner	Art Unit	
	David Lukton	1653	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *21 March 2003* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3-9 and 11-18* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1, 3-9, 11-18* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☒ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

Pursuant to the directives of paper No. 22 (filed 3/21/03), claims 1, 3, 5, 8, 9, 14 have been amended. Claims 1, 3-9, 11-18 remain pending. Claim 4 is now rejoined with the elected group. Claims 1, 3-9, 11-18 are examined in this Office action.

Applicants' arguments filed 3/21/03 have been considered and found persuasive in part. The rejection of claim 1 over Kyoko (JP 06172385) is withdrawn, as is the rejection of claim 14 under 35 U.S.C. §112 1st paragraph.

*

The following is a quotation of the first paragraph of 35 U.S.C. §112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it in such full, clear, concise and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 8-9 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claim 9 recites that as a consequence of producing an anxiolytic effect, broncho-constriction is inhibited. It may be the case that descriptive support exists for producing an anxiolytic effect as a consequence of antagonizing NK-2 receptors, or that descriptive support exists for inhibiting bronchoconstriction as a consequence of

antagonizing NK-2 receptors. However, it does not appear that there is any description of bronchoconstriction being inhibited as a consequence of producing an anxiolytic effect.

Claim 8 recites that as a consequence of treating intestinal spasms, spasms of the biliary tract, spasms of the bladder, spasms of the ureter, kidney infections, or colics, that bronchoconstriction is inhibited. However, there does not appear to be descriptive support for such an assertion. It is requested that the relevant passage(s) be cited.

*

Claims 8 and 9 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

In the specification (p. 27) it is asserted that "the compounds of the invention" have been subjected to *in vitro* assays, as described on page 27 (and references cited therein). It is also asserted (specification) that "the compounds of the invention" were "active" in the assays. The rejected claims assert that therapeutic efficacy can be achieved by administering the claimed compounds. However, there is no evidence that this is the case. Merely because the asserted antagonism may take place *in vivo* does not mean that there exists a single disease or disorder for which benefit will accrue

to a patient. The degree of antagonism might not be sufficient to achieve a perceptable effect; moreover, the NK-2 receptor might not be a critical element in any of the recited disorders, i.e., even if the NK-2 receptor could be blocked to the extent of 100% *in vivo*, it does not necessarily mean that the symptoms of any disease will recede.

The fact is that, whether has shown antagonism of a receptor or stimulation of the same, extrapolation from this to treatment of diseases leads to "unpredictable" results. As stated in *Ex parte Forman* (230 USPQ 546, 1986) and *In re Wands* (8 USPQ2d 1400, Fed. Cir., 1988), the factors to consider in evaluating the need (or absence of need) for "undue experimentation" are the following: quantity of experimentation necessary, amount of direction or guidance presented, presence or absence of working examples, nature of the invention, state of the prior art, relative skill of those in that art, predictability or unpredictability of the art, and breadth of the claims.

In an earlier Office action, the following references and accompanying teachings were cited by the examiner:

- Torsello, Antonio (*Endocrinology* **143** (5) 1968, 2002) pertains to growth hormone, and discloses that stimulation of the growth hormone secretagogue receptor does not correlate with capability to stimulate GH secretion.

- McFadyen "Modifications of the cyclic mu receptor selective tetrapeptide Tyr-c[D-Cys-Phe-D-Pen]NH_2 (Et): effects on opioid receptor binding and activation" (*Journal of Peptide Research* (2000 Mar) 55 (3) 255-61) reported on modifications to the title peptide. The reference discloses that potency changes did not always correlate with affinity, suggesting that the conformation required for binding and the conformation required for activation of the opioid receptors

are different.

- Keith , "mu-Opioid receptor internalization: opiate drugs have differential effects on a conserved endocytic mechanism in vitro and in the mammalian brain" (*Molecular Pharmacology* **53** (3) 377-84, 1998) discloses that the different effects of individual agonists are not correlated with their potencies for receptor activation and that a variety of clinically important agonists differ significantly in their relative abilities to stimulate the rapid internalization of opioid receptors.

- Xiao (*Biochemistry* **40**, 2860, 2001) has looked at the relationship between cAMP production in cells, and *in vivo* activity. While some degree of correlation was noted, a 1:1 correspondence was absent. As stated on page 2864, col 2, "the results indicated that these functions may be dissociated, mostly likely to additional determinantants of *in vivo* activity...". For example, as conveyed in table 6, Phe'-GLP-1 exhibited decreased receptor activation compared with WT GLP-1 along with decreased *in vivo* insulinotropic activity; by contrast, Acetyl-GLP-1 exhibited decreased receptor activation compared with WT GLP-1 accompanied by an increase in *in vivo* insulinotropic activity. Thus, receptor activation is not necessarily predictive of *in vivo* activity.

- Lunec, "MSH receptor expression and the relationship to melanogenesis and metastatic activity in B16 melanoma" (*Melanoma Research* (1992 May) 2 (1) 5-12) compared the effects of different pro-opiomelanocortin (POMC) peptides on melanogenesis and metastasis and their relationship to MSH receptor expression in B16F1 melanoma cells. The authors disclose that the relative binding affinities of the different peptides, measured by displacement of [125I]-Nle4-D-Phe7-alpha-MSH, did not closely correlate with the relative potencies in stimulating melanogenesis and metastasis. This suggests that receptor activation and the subsequent biological response is not determined solely by binding affinity.

The teachings of the foregoing references (Torsello, McFadyen, Keith, Xiao and Lunec) are consistent with the examiner's position that one cannot predict therapeutic efficacy on the basis of *in vitro* activity.

Consider also the following references:

- Foster, P. S. (*Clinical and Experimental Allergy* **29** (1) 12-6, 1999) discloses (page 13, col 1) that anti-IL-4 mAb's are effective in attenuating airway hyperresponsiveness if administered during the primary sensitization phase, but not during the period or direct provocation of the airways with allergen. This raises the issue of the timing of administration of the potentially "active agent", and raises the possibility that, even if the claimed compounds are effective to inhibit bronchoconstriction if administered before allergen challenge, they might not be effective if administered after symptoms of bronchoconstriction had already developed. The claims encompass both possibilities.

- Henderson (*J. Immunol.* **164**, 1086-95, 2000) discloses that administration of soluble IL-4 receptor (sIL-4R) prior to OVA challenge inhibited the inflammatory response, but only if administered intranasally. If administered i.p., the sIL-4R was not effective. This raises the possibility that even if the claimed compounds are effective to inhibit bronchoconstriction if administered directly to the lung, they might not be effective if adminstered orally. The claims encompass both possibilities.

- Wallace J. L. (*Regulatory Peptides* **73** (2) 95-101, 1998) discloses a compound that is, on the one hand an antagonist of neurokinin receptors, but on the other hand, was not effective to treat colitis.

- Fahy J. V. (*American Journal of Respiratory and Critical Care Medicine* **152** (3) 879-84, 1995) discloses that a neurokinin receptor antagonist was not effective to treat asthma.

- Evangelista S. (*Neuropeptides* **30** (5) 425-8, 1996) discloses that a neurokinin receptor antagonist was not effective to treat colitis.

- Reinshagen M. (*Journal of Pharmacology and Experimental Therapeutics* **286**(2) 657-61, 1998) discloses that a neurokinin receptor antagonist was not effective to treat colitis.

- Girard V (*European Respiratory Journal* 8 (7) 1110-4, 1995) discloses that SR 140333 is a neurokinin receptor antagonist which is not effective as an antitussive.

- Biyah K (*European Journal of Pharmacology* 308 (3), 325-8, 1996) discloses a neurokinin receptor antagonist which is not effective to treat asthma.

Accordingly, even when NK-2 receptors can be antagonized *in vitro*, it does not follow that one can predict efficacy in the treatment of asthma, coughing, pulmonary irritation, intestinal spasms, spasms of the biliary tract, spasms of the bladder, spasms of the ureter, kidney infections, or colics. It follows that "undue experimentation" would be required to practice the invention of claims 8 and 9.

In the response filed 3/21/03, no comment has been offered with respect to the propriety of this rejection. Instead, it is argued that the amendments to claims 8 and 9 overcome this ground of rejection. However, claim 8 recites that the compound of claim 7 can be administered for a time and under conditions effective to treat asthma, coughing, pulmonary irritation, intestinal spasms, spasms of the biliary tract, spasms of the bladder, spasms of the ureter, kidney infections, or colics; claim 9 recites that the compound of claim 7 can be administered for a time and under conditions effective to produce an anxiolytic effect. Clearly, each of claims 8 and 9 assert that therapeutic efficacy can be achieved by administered one or more of the claimed compounds. As indicated above, "undue experimentation" would be required to achieve therapeutic efficacy of a compound based only on a finding that the compound can antagonize an

NK-2 receptor *in vitro*.

The rejection is maintained.

*

Claims 1, 3-9, 11-18 are rejected under 35 U.S.C. §112 second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

- In claim 1, 24th line from last, the following is recited:

  "L is a chemical bond **of** CH_2"

  It appears that the conjunction "or" is intended, rather the the preposition "of".

- Claim 4 should begin with the indefinite article (i.e., **A** process).

- In claim 4 (page 35, line 9) it is recited that amino acids are made to react "as shown in the diagram". However, reference to the diagram should be deleted from the claim, and relevant information from the diagram imported into the claim.

- In claim 4 (last two lines), it is recited that the "final monocyclic compound 10" is obtained. However, the claim should make clear how one obtains the compound of formula I once in possession of the "final monocyclic compound 10".

- Claim 14 recited that a patient is afflicted with not just one or two diseases, but fully nine different diseases or disorders. It is suggested that "and" be changed to "or" just before the recitation of "kidney infections".

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a). The practice of automatically extending the shortened statutory period an additional month upon filing of a timely first response to a final rejection has been discontinued by the Office. See 1021 TMOG 35.

A SHORTENED STATUTORY PERIOD FOR RESPONSE TO THIS FINAL ACTION IS SET TO EXPIRE THREE MONTHS FROM THE DATE OF THIS ACTION. IN THE EVENT A FIRST RESPONSE IS FILED WITHIN TWO MONTHS OF THE MAILING DATE OF THIS FINAL ACTION AND THE ADVISORY ACTION IS NOT MAILED UNTIL AFTER THE END OF THE THREE MONTH SHORTENED STATUTORY PERIOD, THEN THE SHORTENED STATUTORY PERIOD WILL EXPIRE ON THE DATE THE ADVISORY ACTION IS MAILED AND ANY EXTENSION FEE PURSUANT TO 37 CFR 1.136(a) WILL BE CALCULATED FROM THE MAILING DATE OF THE ADVISORY ACTION. IN NO EVENT WILL THE STATUTORY PERIOD FOR RESPONSE EXPIRE LATER THAN SIX MONTHS FROM THE DATE OF THIS FINAL ACTION.

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David Lukton whose telephone number is 703-308-3213. The examiner can normally be reached Monday-Friday from 9:30 to 6:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christopher Low, can be reached at (703) 308-2923. The fax number for the organization where this application or proceeding is assigned is 703-872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

D. Lukton 5/16/03

Christopher S. F. Low

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